

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 19, 2009 has been entered. Claim(s) 1, 3, 5-10 and 19-22 are pending and under examination.

### ***Claim Rejections - 35 USC § 112 - Indefiniteness***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claim(s) 1, 3, 5-10, 19, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Claim 1 recites the limitation "the target nucleic acid" in the final "wherein" clause. There is insufficient antecedent basis for this limitation in the claim. The claim language recites "the exposed target nucleic acid" prior to the above limitation.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

**Claims 1, 3, 9, 10, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Hu (U.S. 5,939,251).**

With regard to claims 1, 9, and 10, Hu teaches method of performing in situ PCR within a solid support having multiple compartments, wherein the cells are directly fixed on the solid support (fig. 3-6; col. 5-7, for example). Specifically, Hu teaches method comprising: fixing a cell-containing sample on divided compartments of a support (fig. 6; col. 5, lines 35-45; teaches fixing cells on the bottom wall (slide) of multiple defined compartments, for example); pre-treating the sample to expose the nucleic acid to the sample surface (the teaching of in situ PCR necessarily means the cell sample was treated in some manner to allow amplification); performing PCR amplification of exposed nucleic acids contained in the sample by placing a PCR mixture, containing primers for amplifying a target nucleic acid, into the compartments of the support (col. 6, lines 1-25; teaches providing PCR reagents to multiple compartments and thermal cycling, for example); determining whether amplified nucleic acids in a PCR solution

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contains contain the target nucleic acid (col. 6, lines 25-35; teaches further identification of amplified nucleic acids, for example).

With specific regard to the term "expose" and phrases thereof, the term is not defined by the specification such that it necessarily means the nucleic acid to be amplified migrates or diffuses outside of the cell. Thus, the claimed invention does not require amplification o target nucleic acid outside of the cell. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

With regard to claim 3, the teaching of in situ PCR necessarily means the cell sample was treated in some manner to allow amplification. Nevertheless heating to denature nucleic acids prior to actual extension of new products for PCR encompasses such a limitation.

With regard to claim 19, Hu teaches the slide as able to fit within a thermal cycling apparatus (col. 6, lines 15-25, GeneAmp, for example).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

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the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**1. Claims 5 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hu (U.S. 5,939,251) in view of Villeponteau et al. (U.S. 5,776,679).**

The teachings of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach the labeling of nucleic acids during PCR or detection of PCR products through electrophoresis.

With regard to claim 5, Villeponteau provides a supportive disclosure that teaches labeling nucleic acids during in situ PCR through the incorporation labeled nucleotides (col. 42, lines 50-65, for example). The reference highlights that labeled nucleotides prevent leakage of PCR products.

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a skilled artisan at the time of invention to incorporate labeled nucleotides into in situ the

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PCR of Hu since the prior art expressly suggests such a modification to prevent leakage of PCR products.

With regard to claim 20, the detection of PCR products through electrophoresis was well known as a standard method of PCR product detection. Villeponteau teaches such an electrophoresis method (col. 31, example 3, for example).

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to detect the PCR products of Hu by electrophoresis since the prior art recognized such a modification as standard within the art.

**2. Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hu (U.S. 5,939,251) in view of Villeponteau et al. (U.S. 5,776,679) as applied to claim 5, and in further view of Stapleton et al (US 6,103,192).**

The previously applied reference(s) do not expressly teach the detection of labeled PCR products through hybridization to immobilized probes in microarray format.

Stapleton provides a supportive disclosure that teaches a method wherein various biological specimens are collected, dried, transported, stored and processed on matrixes which adhere cells and viruses. The method involves fixing such samples to the matrixes, exposing the samples by heating them (col.17, lines 31-32, for example), applying the matrixes to thin-walled tubes for amplification (col. 17, lines 23-35; col.22, example 22, for example), and detection by either gel electrophoresis (col.17, lines 10-

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15; col.22, example 22, for example), or by applying the amplified product and detector probes to a probe array comprising capture oligonucleotides (col.16, lines 9-60; col.24, lines 21-50, example 7, for example). Furthermore, Stapleton states that such a detection system eliminates the need for gel electrophoresis, less amplification product is needed as the sensitivity of the detection increases, and allows for multiple oligonucleotide sequences at different array positions to be analyzed in the same detection reaction (col.16, lines 26-28, 57-59).

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to detect the PCR products of Hu through use of immobilized probes in a microarray format since the prior art expressly suggested such a modification to allow for the analysis of multiple sequences at once.

**3. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nuovo et al. (Genome Res. 1993 2: 305-312) in view of Hu (U.S. 5,939,251).**

Newly added claims require that amplified nucleic acid exist in the PCR solution outside of the cell (see "determining" and "detecting" step). With regard to the "fixing", "pre-treating", and "performing" steps, Nuovo teaches performing in situ PCR (pg. 305-306, materials and methods, for example). With regard to detection of amplified nucleic acids existing outside of cells, the reference expressly teaches,

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"... the amplifying solution was retrieved, its DNA separated on an agarose gel, and DNA sequences homologous to the internal fragment of the bcl-2 gene were analyzed using a 32p-labeled probe and Southern hybridization (pg. 307; see also fig. 1A),..., the present study showed that amplification occurred in ethanol- and acetone-fixed cells, but PCR product was primarily detectable in the amplifying solution (pg. 309)."

Nuovo does not expressly teach divided compartments of a support.

The teachings of Nuovo have been outlined above. The reference further highlights,

"The techniques as disclosed can flexibly define a sealed space for carrying out certain molecular biological reactions therein such that wastes of expensive reagents required for the reactions can be reduced because the sealed space can be more conveniently reconfigured depending on the volume of the reaction samples and the space necessary for carrying out each reaction. Furthermore, the enclosure materials can be conveniently and safely removed after completion of the reactions such that the main purposes of the reactions can be achieved without being limited by difficulties caused by post-reaction processes. Because that a secure and flexible sealed configuration is created, large number of the same type of sealed spaces can be conveniently and simultaneously provided and the amplification and detection processes during and after the reactions can be flexibly carried out without being limited by the concerns that leakage or breaks of the sealed spaces may occur in conducting the detection or reaction processes (col. 8)."

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to utilize the products and methods of Hu to perform the in situ PCRs methods of Nuovo since the prior art expressly recognizes that the such PCRs could be performed more efficiently within such products.

### **Conclusion**

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**No claims are allowed.**

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Down et al. (U.S. 5,856,145); recognizes that amplification may be performed directly in lysate.

Hyldig-Nielsen et al. (U.S. 5,888,733); recognizes that in situ PCR products may leak out of cells and serve as templates for further amplification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 814-880-9945. The examiner can normally be reached on Monday-Friday 10:00AM to 6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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